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Streamlining Patient-Reported Outcome (PRO) Data Standardization & Analysis

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ABSTRACT

Patient-reported outcome (PRO) measures is one of the Clinical Outcome Assessments (COA) measures with the aim to capture health-related quality of life from a patient's perspective and without the interpretation of caregivers in contemporary clinical trials. Today, the preferred mode for the collection of PRO data in clinical research is electronic. This preference is driven by the factors like enhancements to data quality that ePRO data collection affords, real-time monitoring, less missing data, and the possibility for immediate interactions. These quality enhancements are compromised using inconsistent data structures and non-adherence to establish data standards.

Currently, PRO data are not required to follow a standard model, and the data models used often vary by COA provider and sponsor. Due to non-uniformity in data structure, it often poses risks for programming, analysis, and challenges in submission activities. The intent of this paper is to provide available information/guidelines on PRO analysis mainly in Oncology therapeutic area (TA). This paper primarily focuses on addressing these issues by discussing/suggesting the best practices like adopting CDISC standards at the source within the ePRO data platform. We will discuss available SDTM standards & ADaM structure based on objectives & endpoints for PRO data analysis.

INTRODUCTION

PRO plays an important role in understanding patient's health conditions, capturing their perspectives on symptoms, quality of life, and treatment satisfaction. Over the past few decades, numerous PRO measures (questionnaires) and guidelines have been developed to ensure consistency and meaningful data collection. However, the current guidelines face some limitations:

1. **Variability in Guidance**: There is a plethora of available guidance, making it challenging to select the most appropriate one. Novices often struggle to understand which guidance to follow for their specific context.

2. **Lack of Standardization**: Although CDISC standards are used in clinical trials to ensure consistency in data collection, ePRO data (electronic PRO data) are not universally required to follow a standard model. The data models used often vary by eCOA (electronic Clinical Outcome Assessment) provider and sponsor.

Standardization of PRO data sets in clinical trials is crucial for ensuring consistency in data collection, analysis, and interpretation. We are focusing on some of the best practices for PRO data collection & established CDISC standards for regulatory submissions of data analysis & reporting.

One of the most developed and standardized TA for PRO data is Oncology. The principles & applications described here may apply to all other TAs as well. However, there is still a need to have a more tailored approach to develop the standards based on different TAs.

In this paper we are illustrating examples of EORTC's QLQ-C30 questionnaire.

RECOMMENDATION OF BEST PRACTICES FOR PRO DATA COLLECTION

DIGITALIZATION

Digitalization has significantly transformed the landscape of clinical trials. Initially, most PRO questionnaire was paper based wherein the data entered by the patient on paper forms were transcribed manually onto electronic databases. This caused several errors in data transfer, issues with data security, and inaccurate information as the data was not usually entered by the patients at the time of occurrence of signs/symptoms. The advent of technology, improved availability and accessibility to the internet, and increased patient comfort with the use of mobile technology have led to the acceptance of electronic PROs in clinical trials. An ePRO is a digital version of a PRO and is used to measure the efficacy and safety of health interventions. Various technologies such as mobile devices (smartphones, tablets), computers, interactive voice response systems (IVRS) are deployed to capture information about a patient's health status and can be in the form of ePRO.

Advantages of ePROs:

- Time-savings as they eliminate the steps associated with transferring information entered on paper records to databases which are often error-prone.
- Improved patient compliance through patient alerts and reminders.
- Improved data quality as the data is entered by the patients in a timely manner and not just at the end of the trial or before the visit.
- Data completeness through mandatory fields and validation checks allows for more thorough and complete data capture.
- Allows for real-time data capture and monitoring of adverse events.
- Improved regulatory compliance.

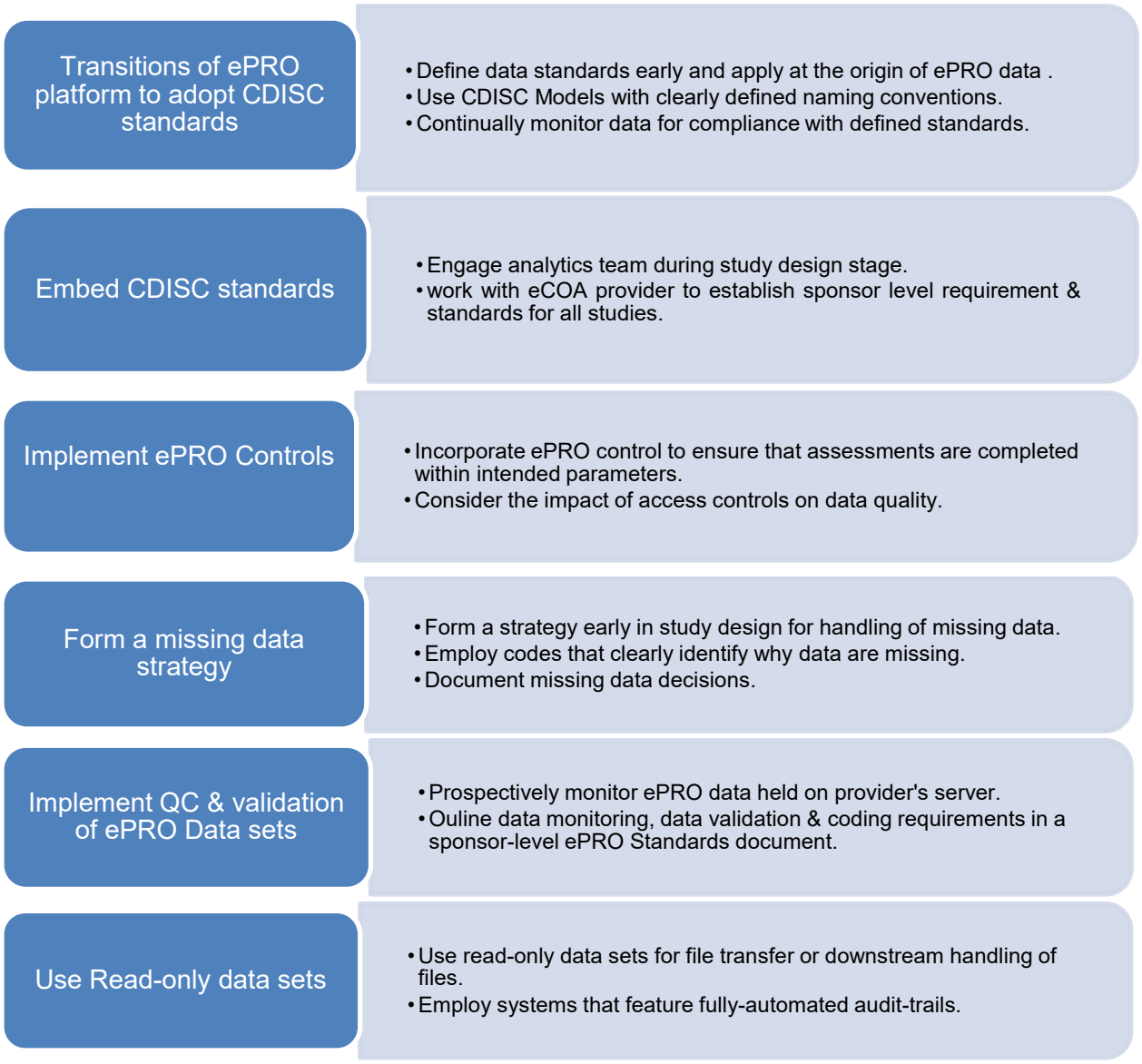
STANDARDIZATION (AT SOURCE)

CDISC standard for ePRO/PRO data sets is not established enough as there is huge gap between the guidelines for collecting ePRO data & submission requirements. Efforts in terms of resources & time needed to transform ePRO collected data in CDISC format (SDTMs/ADaMs) is extensive & need detailed review to ensure correctness of the transformed data.

Adopting the CDISC standard at source within ePRO data platform, ePRO providers-built databases need no or minimal data mapping which is one of the best approaches to implement the SDTM & ADaM standards with better quality. It should be noted that creation of a fully conformant study data tabulation model (SDTM) from ePRO data alone will not always be possible, essential data points will be collected elsewhere, such as the study start date being recorded in the case report form (CRF) rather than the ePRO system, which may prevent calculation of study day, a required value in the SDTM data set. Implementing robust and well-defined data collection, handling, and management procedures would allow a straight-forward transition from ePRO database to SDTM and ADaM data sets and maintain the inherent quality of data submitted to regulators. The use of CDISC standards and controlled terminology allows variables to be coded at the

measure, domain, item, and participant level, which allows logic-based or algorithmic programming (vs hard coding) of data sets, again reducing risk to data quality.

Figure 1. Best practices for ePRO standardization



STANDARDIZATION

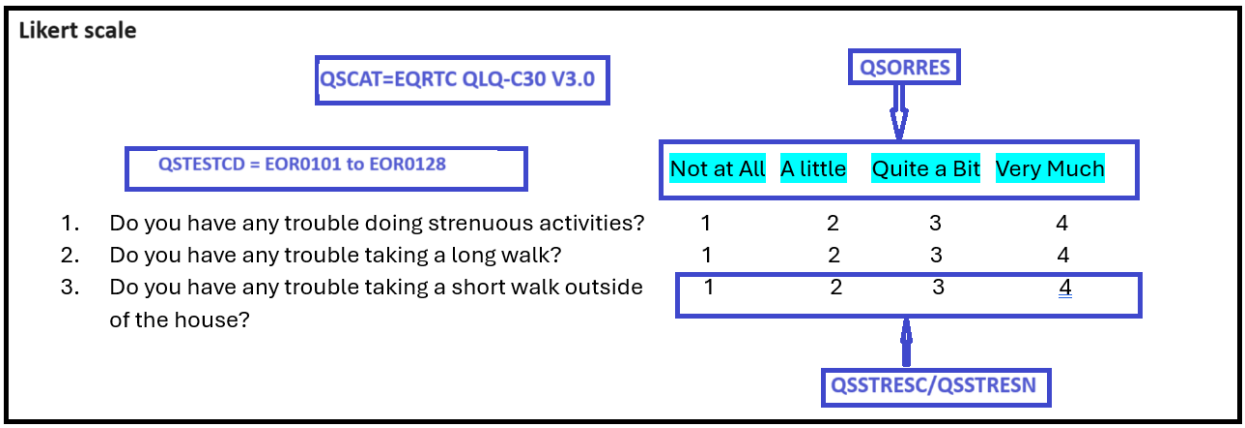
SDTM MAPPING

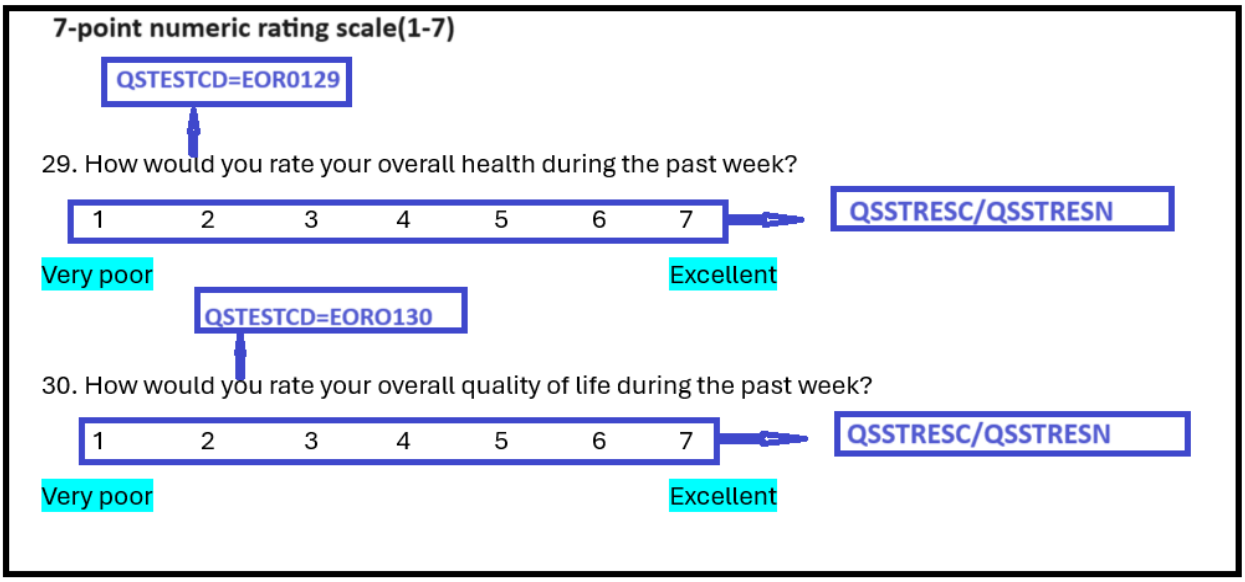
When it comes to SDTM, all the PRO data is mapped to QS domain as most of it is in form of questionnaire with defined set of possible response. CDISC develops SDTMIG (tabulation) QRS supplements that provide information on how to structure the data in a standard format for public domain and copyright-approved instruments. An instrument is a series of questions, tasks or assessments used in clinical research to provide a qualitative or quantitative assessment of a clinical concept or task-based observation. Over the years, more than 100 SDTM QRS supplements have been created to provide standards for collection and

storage of response from questionnaires, rating, and scales.

For example, for the instrument EORTC QLQ-C30, CDISC developed QSTESTCD and QSTEST for each item based on the actual text on instrument. The CDISC documentation of this instrument consists of: (1) controlled terminology, (2) standard database structure with examples, and (3) CRF(s) annotated with the CDISC SDTMIG variables with submission values.

To elaborate PRO data standards & respective analysis further, we will consider example of EQRTC QLQ-C30 V3.0. The EORTC QLQ-C30 V3.0 is a multiple-choice instrument that clinicians may use to assess the quality of life of cancer subjects. It consists of 28 items, each rated on a 4-point Likert scale, plus 2 items rated on a 7-point numeric rating scale. The scale points include a 4-point Likert scale (1-4) and a 7-point numeric rating scale (1-7), with a definition of what is represented by the rating (e.g., 1 = "Not at all").





For EORTC QLQ-C30 V3.0, QSORRES is populated with the text description while the numeric rating is represented in the standardized character and numeric result variables QSSTRESC and QSSTRESN.

The EORTC QLQ-C30 V3.0 instrument includes a Global health status/QoL, 5 Functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning), and 9 Symptom scales (Fatigue, Nausea and vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial difficulties) scores not represented on the CRF, but described in the user manual that are considered as captured data on the CRF and are not considered as derived in the example

below. These scores may be submitted in SDTM or derived in the Analysis Data Model (ADaM) per scoring instructions from the user manual.

Table 1. Example SDTM.QS data for EORTC QLQ-C30 V3.0 instrument

USUBJID	VISITNU	VISIT	QSDTC	QSCAT	QSTESTCD	QSTEST	QSORRES	QSSTRESC	QSSTRESN	QSSTRESU
AB1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0101	EOR01-Trouble Doing Strenuous Activities	A LITTLE	A LITTLE	2	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0102	EOR01-Trouble Taking Long Walk	A LITTLE	A LITTLE	2	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0103	EOR01-Trouble Taking Short Walk Outside	NOT AT ALL	NOT AT ALL	1	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0104	EOR01-Stay in Bed/Chair During the Day	QUITE A BIT	QUITE A BIT	3	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0105	EOR01-Need Help Eating/Dressing/Washing	NOT AT ALL	NOT AT ALL	1	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0106	EOR01-Limited in Work/Daily Activities	A LITTLE	A LITTLE	2	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0107	EOR01-Limited Hobbies/Leisure Activities	NOT AT ALL	NOT AT ALL	1	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0108	EOR01-Were You Short of Breath	A LITTLE	A LITTLE	2	
AB 1001 10012002	80	WEEK1	2019-01-07T16:23:08	EORTC QLQ-C30 V3.0	EOR0109	EOR01-Have You Had Pain	A LITTLE	A LITTLE	2	

ENDPOINT BASED ANALYSIS & ADAM CREATION

ADaM defines data set and metadata standards that support efficient generation, replication, and review of clinical trial statistical analyses. Below is the list of endpoints & respective statistical analysis we perform based on the endpoint for PRO data.

PRO data analysis based on endpoints:

Objectives & Endpoints for PRO data	Type of Response Variable type	ADaM	Anaysis Method
Summary of Individual scores/Sub-scores & Change from Baseline in scores	Continuous Variable	ADQS	Descriptive statistics(n, Mean,Standard Deviation,Median,Min-Max) by timepoints for respective parameter.
	Categorical Variable		Count and percent for each response by timepoints.
Comparision for change from baseline across treatment	Continuous Variable	ADQS	ANOVA or MMRM (Mixed model for repeated measures).
	Categorical Variable	ADQS	Odds Ratio/Mantel-Haenszel Test.
Completion rate	Categorical Variable	ADQS	Count & percent of completers for the PRO questionaure. Falls in the analysis of study conduct, where the rate of completion is defined at each scheduled timepoint/visit of the PRO questionaire administration. This analysis describes the magnitute of missing data in the PRO data collection.
Time to event analysis	Continuous Variable	ADTTEQS	Median time to event and confidence interval, percentile, propertion of events/censored, hazard ratio, cofidence interval, p-value

Fundamentals of ADaM for BDS structure:

One of the basic intents of creating CDISC compliant analysis data set is to provide traceability from analysis data sets to the records in respective SDTMs. One can try to follow naming conventions used in BDS standard for PRO data sets as long as QRS supplements have not been provided by CDISC.

It is preferable for QS domain to be split into separate analysis data sets (ADaMs) for each individual questionnaire, rating, or scale. These instruments are analyzed separately, and the associated data sets may be rather large. In addition, scoring calculations may vary widely for different questionnaires, so separating them simplifies the programming logic, and makes them easier to use.

ADQS (Analysis data set for EORTC-QLQ-C30):

SDTM.QS to ADQS OR AD<xxxxxx> (Direct mapping from SDTM to ADaM)

QS	ADQS or ADPRO	Comments
QSCAT	PARCAT1	
QSSCAT	PARCAT2	If expected sub-scale derivation
QSTEST	PARAM	
QSTESTCD	PARAMCD	
QSSTRESN	AVAL	If PARAMCD is not derived

We most of the time create two efficacy data sets (ADQS and ADTTEQS) for PRO data, both use ADaM Basic Data Structure (BDS) and have a data structure of one record per subject per parameter per visit.

Below is the screenshot of ADQS data sets with parameters directly coming from SDTM.QS. Example we provided in screenshot (Table 1- Table 4) focusing on flow from mapping collected data to SDTM.QS and then to respective ADaMs.

Table 2. Example ADQS data for EORTC QLQ-C30 V3.0 instrument which are directly assigned from SDTM.QS

USUBJID	PARCAT2	PARAMC	PARAM	PARAMTYP	AVISIT	VISIT	AVAL	AVALC	BASE	BASEC
AB 1001 10012002	Functional Scales QLQ-C30	EOR0101	101		BASELINE [Week 1]	WEEK1	2	A LITTLE	2	A LITTLE
AB 1001 10012002	Functional Scales QLQ-C30	EOR0102	102		BASELINE [Week 1]	WEEK1	2	A LITTLE	2	A LITTLE
AB 1001 10012003	Functional Scales QLQ-C30	EOR0101	101		BASELINE [Week 1]	WEEK1	3	QUITE A BIT	3	QUITE A BIT
AB 1001 10012003	Functional Scales QLQ-C30	EOR0101	101		Week 5	WEEK5	3	QUITE A BIT	3	QUITE A BIT
AB 1001 10012002	Functional Scales QLQ-C30	EOR0103	103		BASELINE [Week 1]	WEEK1	1	NOT AT ALL	1	NOT AT ALL
AB 1001 10012002	Functional Scales QLQ-C30	EOR0104	104		BASELINE [Week 1]	WEEK1	3	QUITE A BIT	3	QUITE A BIT
AB 1001 10012003	Functional Scales QLQ-C30	EOR0102	102		BASELINE [Week 1]	WEEK1	3	QUITE A BIT	3	QUITE A BIT
AB 1001 10012003	Functional Scales QLQ-C30	EOR0102	102		Week 5	WEEK5	4	VERY MUCH	3	QUITE A BIT
AB 1001 10012002	Functional Scales QLQ-C30	EOR0105	105		BASELINE [Week 1]	WEEK1	1	NOT AT ALL	1	NOT AT ALL
AB 1001 10012002	Functional Scales QLQ-C30	EOR0106	106		BASELINE [Week 1]	WEEK1	2	A LITTLE	2	A LITTLE

Table 3. Example ADQS data set for EORTC QLQ-C30 V3.0 instrument with key derived parameters.

USUBJID	PARCAT1	PARCAT2	AVISIT	PARAM	PARAMC	AVAL	BASE
AB 1001 10012002	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	BASELINE [Week 1]	EOR01-Emotional Functioning	EOR01EF	83.33333333	83.33333333
AB 1001 10012002	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	BASELINE [Week 1]	EOR01-Physical Functioning	EOR01PF	73.33333333	73.33333333
AB 1001 10012002	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	BASELINE [Week 1]	EOR01-Role Functioning	EOR01RF	83.33333333	83.33333333
AB 1001 10012002	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	Week 5	EOR01-Emotional Functioning	EOR01EF	66.66666667	83.33333333
AB 1001 10012002	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	Week 5	EOR01-Physical Functioning	EOR01PF	53.33333333	73.33333333
AB 1001 10012002	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	Week 5	EOR01-Role Functioning	EOR01RF	33.33333333	83.33333333
AB 1001 10012003	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	BASELINE [Week 1]	EOR01-Emotional Functioning	EOR01EF	100	100
AB 1001 10012003	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	BASELINE [Week 1]	EOR01-Physical Functioning	EOR01PF	60	60
AB 1001 10012003	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	BASELINE [Week 1]	EOR01-Role Functioning	EOR01RF	33.33333333	33.33333333
AB 1001 10012003	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	Week 5	EOR01-Emotional Functioning	EOR01EF	100	100
AB 1001 10012003	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	Week 5	EOR01-Physical Functioning	EOR01PF	46.66666667	60
AB 1001 10012003	EORTC QLQ-C30 V3.0	Functional Scales QLQ-C30	Week 5	EOR01-Role Functioning	EOR01RF	50	33.33333333

Key derived parameters in ADQS (BDS-structure) data set for EORTC-QLQ-C30

Example specification for Derived parameters “EORTC-QLQ-C30-Physical Functioning”, “EORTC-QLQ-C30-Role Functioning” & “EORTC-QLQ-C30-Emotional functioning” which has been derived using below derivations using individual score.

Variable Name	Parameter Code	Parameter	Comments
AVAL	EOR01PF	EORTC-QLQ-C30 Physical Functioni ng	At each Subject/Visit level if at least half the values of QS.AVAL are non- missing where QS.PARAMCD in ('EOR0101', ' EOR0102', ' EOR0103', ' EOR0104',' EOR0105') then calculate a raw score raw score=mean of the non-missing QS QSSTRESN (i.e. (I1 + I2 + ...In)/n), where n=number of non-missing AVALs) Set AVAL to be (1-(raw score-1)/3)*100
AVAL	EOR01RF	EORTC-QLQ-C30 Role functioning	At each Subject/Visit level if at least half the values of QS.AVAL are non-missing where QS.PARAMCD in (' EOR0106', ' EOR0107') then calculate a raw score raw score=mean of the non-missing QS.QSSTRESN (i.e. (I1 + I2 + ...In)/n), where n=number of non-missing AVALs) Set AVAL to be (1-(raw score-1)/3)*100
AVAL	EOR01EF	EORTC-QLQ-C30 Emotional Functioni ng	At each Subject/Visit level if at least half the values of QS.AVAL are non- missing where QS.PARAMCD in (' EOR0121', '', ' EOR0123', ' EOR0124') then calculate a raw score raw score=mean of the non-missing QS.QSSTRESN (i.e. (I1 + I2 + ...In)/n), where n=number of non-missing AVALs) Set AVAL to be (1-(raw score-1)/3)*100

PRO response transformation

Many times, the PRO questionnaire responses are ordinal. For statistical analysis, such item responses are usually transformed into numerical values. A PRO endpoint may be analyzed at the item level or scale level (e.g., a total score; a transformed scale score ranging from 0 to 100). The scoring methods of a published PRO instrument should be available from the user manual or scoring guideline documents from its publisher. Most of our study protocols have already described their PROs scoring methods when describing PRO endpoints, particularly for those PROs that have been widely used across molecules. For some scales with complex or lengthy scoring rules, they can be described in statistical analysis plan (SAP).

TIME TO DETERIORATION FOR PRO DATA

Time-to-meaningful-deterioration is often an important patient-reported outcome (PRO). Lack of clear PRO research objectives and inconsistency in how PRO data are analyzed makes it difficult to interpret results both within and across trials. While deriving on time to deterioration, we need to focus on 2 important points, 1st is definition of events that is threshold of deterioration and 2nd is censoring rules. These two factors are based on the objective of the trials. For example, if objective is to know if Treatment A delay PRO deterioration or death longer than the Treatment B.

Event definition: First deterioration in PRO endpoint or Death.

Censoring Rule: Disease progression/Discontinuation/withdrawal will be censored.

Time to deterioration of a PROs can vary widely so event definitions should be relevant to the objective of the trial.

Below is the example of ADTTEQS (Analysis Data for Time to event analysis for PRO endpoint) and PARAM "Time to deterioration in Global Health Status/Qol EQRTC QLQ-C30(months). ADaMIG will give detailed list of variables in time to event data set however in below Table 4 we are keeping only variables which will be important to understand the concept with EORTC QLQ-C30 related parameters.

Table 4: Example of ADTTEQS (Time to event data set considering parameter "Time to Deterioration")

USUBJID	PARCAT1	PARAM	PARAMC	AVAL	AVALC	STARTDT	ADT	CNSR
AB 1001 10012002	Deterioration in Global Health Status/QoL EORTC QLQ-C30 - Time to Event	Time to Deterioration in Global Health Status/QoL EORTC QLQ-C30 (months)	PROQ30	1.051334702	1.0513347023	07Jan2012	07Feb2012	0
AB 1001 10012003	Status/QoL EORTC QLQ-C30 - Time to Event	Global Health Status/QoL EORTC QLQ-C30 (months)	PROQ30	0.952772074	0.9527720739	09Jan2012	06Feb2012	1
AB 1001 10012005	Deterioration in Global Health Status/QoL EORTC QLQ-C30 - Time to Event	Time to Deterioration in Global Health Status/QoL EORTC QLQ-C30 (months)	PROQ30	24.80492813	24.804928131	10Apr2012	03May2014	1
AB 1001 10012007	Deterioration in Global Health Status/QoL EORTC QLQ-C30 - Time to Event	Time to Deterioration in Global Health Status/QoL EORTC QLQ-C30 (months)	PROQ30	0.032854209	0.0328542094	24Jul2012	24Jul2012	1
AB 1001 10012008	Deterioration in Global Health Status/QoL EORTC QLQ-C30 - Time to Event	Time to Deterioration in Global Health Status/QoL EORTC QLQ-C30 (months)	PROQ30	37.5523614	37.552361396	09Jul2012	24Aug2015	1
AB 1001 10012009	Deterioration in Global Health Status/QoL EORTC QLQ-C30 - Time to Event	Time to Deterioration in Global Health Status/QoL EORTC QLQ-C30 (months)	PROQ30	6.308008214	6.3080082136	20Aug2012	27Feb2013	1

CONCLUSION

PROs are increasingly recognized by regulators, clinicians, and patients as valuable tools to collect patient-centered data. It provides unique information on the impact of a medical condition and its treatment from the patient's perspective. Following CDISC standards ensures that PRO data is organized, consistent, and interpretable, reducing pushback and delays during regulatory review. Moreover, complete traceability ensures transparency and accountability.

Recommended best practices promote data quality for data collection, representation, and reporting. Standardized data reduces the need for custom transformations and mappings. This cost-effective approach benefits both pharma companies and regulatory bodies. Researchers can focus on innovative approaches rather than grappling with data inconsistencies.

In summary, embracing standardization in PRO data analysis ensures robust, reliable, and harmonized results, benefiting patients, researchers, and regulatory agencies.

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